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Antimicrobial Activity of Tigecycline and Other Broad-Spectrum Agents Tested Against Bacterial Isolates Collected in European Hospitals in 2006

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ABSTRACT

Objective:

To assess the activity of tigecycline against recent bacterial isolates from Europe. Tigecycline is a novel glycylcycline antimicrobial recently approved by the European Medicines Agency for the treatment of complicated skin and skin structure infections (cSSSI) and intra-abdominal infections.

Methods:

Bacterial isolates (non-duplicates) were consecutively collected in 2006 from documented infections in patients hospitalized in 24 medical centers located in Europe (9 countries), Turkey and Israel. The isolates were obtained mainly from patients with bacteremia (BSI; 61.9%), pneumonia (16.1%) and cSSSI (11.1%). Frequency of occurrence of pathogens was determined and their antibiograms assessed using reference broth microdilution methods according to the CLSI M7-A7 (2006). Tigecycline-susceptible (S) breakpoints (US-FDA/EUCAST) were defined as <=2/<=1 mg/L for Gram-negative bacilli; <=0.5/<=0.5 mg/L for staphylococci, and <=0.25/<=0.25 mg/L for streptococci and enterococci.

Results:

A total of 5,032 strains were evaluated and the frequency of pathogen occurrence and susceptibility rates to tigecycline are summarized in the table.

	Cumulative % inhibited at tigecycline MIC (mg/L):							% Susceptible (US-FDA
Organism (no. tested)	≤0.12	0.25	0.5	1	2	4	>4	/EUCAST)
S. aureus (1,478)	80.8	99.5	99.5	-	-	-	-	99.5/99.5
E. coli (854)	77.0	98.0	99.9	100.0	-	-	-	100.0/100.0
Enterococcus spp. (577)	83.4	100.0	-	-	-	-	-	100.0/100.0
Coagulase-negative staphylococci (520)	64.0	97.3	99.8	100.0	-	-	-	99.8/99.8
P. aeruginosa (302)	0.3	1.0	1.7	3.0	9.3	49.3	100.0	-[a]/-[a]
Klebsiella spp. (263)	14.4	73.0	92.4	98.5	100.0	-	-	100.0/98.5
Beta-haemolytic streptococci (235)	100.0	-	-	-	-	-	-	100.0/100.0
Enterobacter spp. (167)	4.2	58.7	84.4	95.2	98.8	100.0	-	98.8/95.2

a. No breakpoints have been established by the US-FDA or EUCAST.

Tigecycline was highly active against the top 8 pathogens, except for *P. aeruginosa* (PSA). Among the 4 most common indicated pathogens (3,430 strains; 68.0% of the total), tigecycline was active against >99% at the US-FDA/EUCAST S breakpoints. The main resistance phenotypes detected were methicillin-resistant (R) *S. aureus* (31.4%) and CoNS (74.6%), ciprofloxacin-R *E. coli* (20.6%), extended-spectrum beta-lactamase (ESBL)-screen-positive *Klebsiella* spp. (22.8%) and *E. coli* (6.3%), imipenem-R PSA (IRPSA; 24.2%) and vancomycin-R enterococci (5.0%). Tigecycline showed excellent activity against these R pathogens, except IRPSA.

Conclusions:

Tigecycline exhibited a wide-spectrum of activity and potency versus contemporary BSI isolates collected in Europe. R to tetracycline or other antimicrobial classes did not adversely influence tigecycline activity. Treatment options for serious infections in the nosocomial environments should benefit from the availability of the new antimicrobial class agent, tigecycline.

INTRODUCTION

Tigecycline is the first glycylcycline antibiotic to be approved by the US Food and Drug Administration (FDA). Tigecycline has also been recently approved by the European Medicines Agency (EMEA) for treatment of complicated skin and soft tissue infections (cSSTI) and intra-abdominal infections.

The compound is a semisynthetic 9-t-butylglycylamido derivative of minocycline. The position 9 substitution of tigecycline, however, provides additional steric hindrance features that result in a greater spectrum of activity. Thus, the drug overcomes the 2 major resistance mechanisms of the related tetracyclines: drug-specific efflux pump acquisition and ribosomal protection.

Tigecycline has demonstrated activity against many gram-positive and -negative organisms, including methicillin-resistant *Staphylococcus aureus,* vancomycin-intermediate and -resistant enterococci, and extended-spectrum ß-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae.* It is also active against many anaerobic bacteria, as well as atypical pathogens, including rapidly growing, non-tuberculous mycobacteria. The present study was conducted to evaluate the activity of tigecycline against recent bacterial isolates from across Europe.

MATERIALS AND METHODS

Bacterial isolates

Bacterial isolates (non-duplicates) were consecutively collected in 2006 from documented infections in patients hospitalized in 24 medical centers located in Europe (9 countries), Turkey and Israel. The isolates were obtained from hospitalized patients with bacteremia (BSI; 61.9%), pneumonia (16.1%) and cSSSI (11.1%), among other infections. Frequency of occurrence of pathogens was determined and their antibiograms assessed using reference broth microdilution methods according to the CLSI M7-A7 (2006).

Susceptibility testing

The isolates were tested for susceptibility against tigecycline and other comparators by broth microdilution methods using validated dry-form panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc.; Cleveland, OH, USA). Testing, incubation and MIC interpretation were performed using the manufacturer's recommendations and/or Clinical and Laboratory Standards Institute (CLSI) guidelines. Tigecycline-susceptible (S) breakpoints (US-FDA/EUCAST) were defined as <=2/<=1 mg/L for Gram-negative bacilli; <=0.5/<=0.5 mg/L for staphylococci, and <=0.25/<=0.25 mg/L for streptococci and enterococci. Quality control was performed using American Type Culture Collection (ATCC) strains including *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619 and *Pseudomonas aeruginosa* ATCC 27853.

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RESULTS

- The in vitro activities of tigecycline and comparator agents are summarized in Tables 1 and 2.
- All *S. aureus* and coagulase-negative staphylococci (CoNS) were susceptible to tigecycline at the susceptible breakpoints established by US-FDA and EUCAST (MIC_{50} of 0.12 mg/L and MIC_{90} of 0.25 mg/L for both organisms).
- Vancomycin was also active against all staphylococcal strains at the susceptible breakpoint while one CoNS strain showed decreased susceptibility to linezolid (MIC of 8 mg/L). Decreased susceptibility to teicoplanin (99.2-96.2% susceptible) and quinupristin/dalfopristin (99.8% susceptible) was also observed among CoNS (Table 1).
- Tigecycline was the most active compound tested against enterococci (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L), and only tigecycline and linezolid (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) were active against all strains at the susceptible breakpoint (100.0% susceptible; Table 1).
- All *E. coli* and *Klebsiella* spp. strains were susceptible to tigecycline at the susceptible breakpoint established by the US-FDA (≤2 mg/L); four *Klebsiella* spp. strains (1.5%) considered susceptible by the US-FDA breakpoints, however, were intermediate by the EUCAST criteria.
- *Klebsiella* spp. strains showed high rates of ESBL phenotype (21.7-22.8%) and only 79.4% of *E. coli* strains were susceptible to ciprofloxacin.
- *Enterobacter* spp. strains exhibited elevated rates of resistance to most antimicrobial agents tested. Tigecycline showed superior potency (MIC_{50}, 0.25 mg/L and MIC_{90}, 1 mg/L) and similar spectrum (95.2-98.8% susceptible) when compared to imipenem (MIC_{50}, 0.5 mg/L; MIC_{90}, 2 mg/L; 95.2-98.8% susceptible).

Table 1. Antimicrobial activity of tigecycline and comparators tested against Gram-positive isolates collected in European medical centers in 2006.

Organism (no. tested)/ antimicrobial agent	MIC (mg/L) MIC_{50}	MIC (mg/L) MIC_{90}	% Susceptible US-FDA/CLSI[a]	% Susceptible EUCAST[b]
S. aureus (1,478)				
Tigecycline	0.12	0.25	100.0	100.0
Tetracycline	≤2	≤2	91.7	-[c]
Oxacillin	0.5	>2	68.6	68.6
Levofloxacin	≤0.5	>4	64.9	64.9
Clindamycin	≤0.25	>2	86.4	-
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.8	-
Quinupristin/dalfopristin	0.5	0.5	99.5	-
Linezolid	2	2	100.0	100.0
Teicoplanin	≤2	≤2	100.0	100.0
Vancomycin	1	1	100.0	100.0
Coagulase-negative staphylococci (520)				
Tigecycline	0.12	0.25	100.0	100.0
Tetracycline	≤2	>8	78.8	-
Oxacillin	>2	>2	25.4	25.4
Levofloxacin	2	>4	44.4	44.4
Clindamycin	≤0.25	>2	76.0	-
Trimethoprim/sulfamethoxazole	≤0.5	>2	61.3	61.3
Quinupristin/dalfopristin	≤0.25	0.5	98.8	-
Linezolid	1	1	99.8	99.8
Teicoplanin	≤2	4	99.2	96.2
Vancomycin	1	2	100.0	100.0
Enterococcus spp. (577)				
Tigecycline	0.12	0.25	100.0	100.0
Tetracycline	>8	>8	36.2	-
Ampicillin	≤1	>16	72.3	-
Levofloxacin	>4	>4	39.7	-
Gentamicin (HL)[d]	≤500	>1000	62.9	62.9
Linezolid	1	2	100.0	100.0
Quinupristin/dalfopristin	>2	>2	21.0	-
Teicoplanin	≤2	≤2	96.4	96.2
Vancomycin	1	2	95.0	95.0
ß-haemolytic streptococci (235)				
Tigecycline	≤0.03	≤0.03	100.0	100.0
Penicillin	≤0.015	0.06	100.0	-
Erythromycin	≤0.25	>2	79.7	-
Clindamycin	≤0.25	>2	89.4	-
Levofloxacin	≤0.5	1	100.0	97.5
Vancomycin	0.5	1	100.0	100.0

a. Susceptibility rates were calculated by applying breakpoints approved by the United States Food and Drug Administration (US-FDA) and/or the Clinical and Laboratory Standards Institute (CLSI).
b. Susceptibility rates were calculated by applying EUCAST breakpoints.
c. - = no breakpoint has been established by the EUCAST.
d. HL = high-level resistance.

- *Acinetobacter* spp. exhibited high rates of resistance to all antimicrobials tested except tigecycline (MIC_{50}, 0.5 mg/L and MIC_{90}, 1 mg/L; 99.1% susceptible) and polymyxin B (MIC_{90}, ≤0.5 mg/L; 99.1% susceptible using Enterobacteriaceae breakpoints). Only 50.0-51.9% of strains were susceptible to imipenem while all strains were inhibited at tigecycline MIC values of ≤4 mg/L. In contrast, tigecycline showed limited activity against *P. aeruginosa* (MIC_{50}, >4 mg/L).

Table 2. Antimicrobial activity of tigecycline and comparators tested against Gram negative isolates collected in European medical centers in 2006.

Organism (no. tested)/antimicrobial agent	MIC (mg/L) MIC_{50}	MIC (mg/L) MIC_{90}	% Susceptible US-FDA/CLSI[a]	% Susceptible EUCAST[b]
E. coli (854)				
Tigecycline	0.12	0.25	100.0	100.0
Cefuroxime	4	8	92.6	92.6
Ceftriaxone	≤0.25	≤0.25	95.0 (5.6)[c]	94.4
Ceftazidime	≤1	≤1	95.9 (6.2)[c]	93.8
Cefepime	≤0.12	0.25	96.1	94.7
Imipenem	0.25	0.25	100.0	100.0
Ciprofloxacin	≤0.03	>4	79.4	79.2
Gentamicin	≤2	≤2	94.1	94.0
Klebsiella spp. (263)				
Tigecycline	0.25	0.5	100.0	98.5
Cefuroxime	<2	>16	74.5	74.5
Ceftriaxone	≤0.25	>32	79.5 (22.8)[c]	77.2
Ceftazidime	≤1	>16	83.7 (21.7)[c]	78.3
Cefepime	≤0.12	>16	88.2	78.7
Imipenem	0.25	0.5	99.2	98.5
Ciprofloxacin	≤0.03	4	84.4	82.9
Gentamicin	≤2	>8	88.6	87.8
Enterobacter spp. (167)				
Tigecycline	0.25	1	98.8	95.2
Cefuroxime	>16	>16	25.1	25.1
Ceftriaxone	≤0.25	>32	68.9	58.7
Ceftazidime	≤1	>16	65.3	56.9
Cefepime	≤0.12	8	94.6	77.2
Imipenem	0.5	2	99.8	95.2
Ciprofloxacin	≤0.03	>4	79.0	76.6
Gentamicin	<2	>8	86.8	86.2
Acinetobacter spp. (108)				
Tigecycline	0.5	1	99.1[d]	-[e]
Cefepime	16	>16	34.3	-
Ceftazidime	>16	>16	29.6	-
Imipenem	2	>8	51.9	50.0
Ampicillin/sulbactam	>16	>16	36.1	-
Ciprofloxacin	>4	>4	21.3	21.3
Amikacin	>32	>32	31.5	28.7
Polymyxin B	≤0.5	≤0.5	99.1	-
P. aeruginosa (302)				
Tigecycline	>4	>4	-	-
Cefepime	4	16	79.8	79.8
Ceftazidime	2	>16	74.8	74.8
Imipenem	2	>8	75.8	75.8
Piperacillin/tazobactam	4	>64	80.1	-
Ciprofloxacin	0.25	>4	69.9	65.6
Amikacin	≤4	16	93.0	88.1
Polymyxin B	1	1	99.7	-

a. Susceptibility rates were calculated by applying breakpoints approved by the United States Food and Drug Administration (US-FDA) and/or the Clinical and Laboratory Standards Institute (CLSI).
b. Susceptibility rates were calculated by applying EUCAST breakpoints.
c. Percentage of isolates with ESBL phenotypes.
d. Rates were calculated by applying breakpoints approved by the US-FDA for Enterobacteriaceae.
e. - = no breakpoint has been established.

CONCLUSIONS

- Tigecycline was highly active against the most frequently isolated bacterial pathogens causing infections in patients hospitalized in European medical centers, except for *P. aeruginosa*.
- Tigecycline appears to be a valuable treatment option for serious infections caused by multidrug-resistant organisms in European medical centers.
- Longitudinal surveillance programs are of great importance in monitoring the in vitro activity of novel compounds following their introduction into clinical practice.